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SUBCONVULSIVE EFFECTS OF 1, 1-DIMETHYLHYDRAZINE ON LOCOMOTOR PERFORMANCE IN THE CAT: RELATIONSHIP OF DOSE TO TIME OF ONSET

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The experiments reported herein were conducted according to the "Principles of Laboratory Animal Care" established by the National Society for Medical Research.

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FOREWORD

This research was performed under Contract AF 33(615)-2822 by the Department of Anatomy and the Brain Research Institute, School of Medicine, University of California, Los Angeles, California 90024. The work was performed in support of Project 6302, "Toxic Hazards of Propellants and Materials," Task 630202, "Pharmacology and Biochemistry," from August 1965 to December 1966, for the Toxicology Branch, Toxic Hazards Division, Biomedical Laboratory, Aerospace Medical Research Laboratories, Wright-Patterson Air Force Base, Ohio.

The experiments were conducted jointly by M. B. Sterman, Ph.D., Research Psychologist, Veterans Administration Hospital, Sepulveda, California, and Assistant Professor in Residence, Departments of Anatomy and Physiology, UCLA, and M. D. Fairchild, Ph.D., Research Pharmacologist, Veterans Administration Hospital, Long Beach, California, and Assistant Professor in Residence, Department of Pharmacology, UCLA. Kenneth C. Back, Ph.D., was contract monitor for the Aerospace Medical Research Laboratories.

The authors gratefully acknowledge the assistance of Mr. H. Dubkin, Senior Electronics Technician, and Miss Ellyn Hittelman, Laboratory Technician, for their contributions to the execution of these experiments. They also wish to acknowledge the important statistical consultation and data reduction services provided by the Western Research Support Center, Veterans Administration Hospital, Sepulveda, California.

This technical report has been reviewed and is approved.

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ABSTRACT

Several recent neurophysiological findings in the study of 1, 1-dimethylhydrazine toxicity have suggested that this substance initiates a gradual increase in central nervous system (CNS) excitability, leading eventually to general convulsions. This process, however, is periodically interrupted by episodes of recovery or suppression of excitability. In the present experiment an attempt was made to investigate the nature of this alternation in response to low doses of UDMH, using the performance of a locomotor task as a measure of CNS effects. Cats were trained and tested in a special runway apparatus to provide a reliable indication of performance changes over a 6 hour period following the administration of 4, 8, and 16 mg/kg UDMH. These low doses significantly altered locomotor performance in a predictable manner. The response to a given dose was both consistent and unique to that dose. Within the 6 hour period of measurement, 16 mg/kg caused a gradual reduction in performance velocity leading to a total disruption, which was then followed by a tendency to recover; 8 mg/kg produced a recurrent depression of velocity followed by an enhancement, and 4 mg/kg resulted in a biphasic depression facilitation response. Other more general findings are also discussed.

SECTION I

INTRODUCTION

In the cat, a characteristic sequence of behavioral and electrophysiological signs has been found to precede the onset of general seizures following the parenteral administration of 1, 1-dimethylhydrazine (UDMH) in a time course directly related to dose (Fairchild and Sterman, 1964). In other neurophysiological studies of this compound, detectable effects were consistently noted at doses well below these convulsive levels (Fairchild and Sterman, 1965). Low dose effects, however, were not accompanied by any overt symptoms of illness. The major difficulty encountered in assessing the behavioral consequences of these low doses was the tendency for performance to become more variable once UDMH was introduced into the situation. To quote a previous communication (Fairchild and Sterman, 1965), "as drug test sessions continued --- all aspects of performance tended to become more labile (although) reasonable periods of time were allowed between drug tests and there was no obvious change in the general physiological condition, weight or feeding patterns of the cats" (page 29). Thus, it would appear that some subtle variable, inherent in the most judicious of behavioral studies on UDMH, has masked any clear determination of preconvulsive effects.

Recent neurophysiological investigations of sensory evoked potentials and monosynaptic reflex activity in response to UDMH exposure have indicated a graded increase in excitability leading eventually to convulsions, but interrupted periodically by episodes of recovery or suppression of activity

(Goff et al., in press). It is possible that such an alternation of central nervous system excitability would confound any biological measurements obtained without prior knowledge of its characteristics. A determination of the subconvulsive effects of UDMH on the central nervous system has been one of the primary objectives of this laboratory, particularly as related to integrated behavior. We, therefore, examined the implications of cyclic alterations in brain excitability in response to UDMH within this context.

SECTION II

METHODS

Five adult cats were trained to stable performance in a runway apparatus designed to detect subtle changes in central nervous system functions. Integrated locomotor behavior may be easily quantified in this runway by reference to the time required to run, alternately, between two enclosed chambers (Fig. 1). The apparatus and training procedures employed have been described in detail elsewhere (Fairchild and Sterman, 1965; Sterman and Fairchild, 1966).

Figure 1

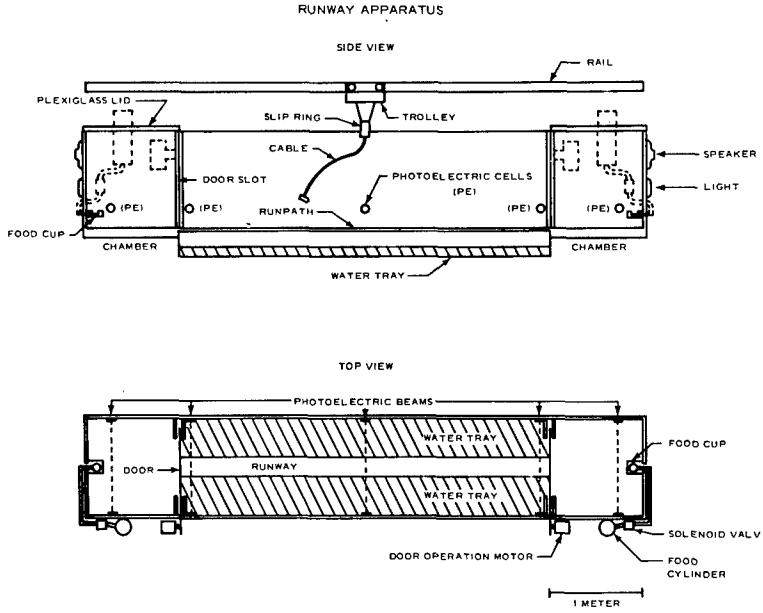

Figure 1: Diagram of side and top view of runway apparatus. The two chambers are identical and serve alternately as start and goal boxes as the animal runs between them. Note photoelectric cells along run-path which were used to time performance. Mirrors suspended overhead were used to observe behavior during the experiments.

To achieve the objectives of the present experiment, the five animals were run in a predetermined sequence which spanned a period of approximately 6 hours following the injection of either 1 cc of normal saline, or various doses of UDMH. Animals were started at periods of 30, 90, 150, 210, and 270 minutes following injection. Each of the five cats was run 60 trials and their starting time sequence was rotated in a counter-balanced design so that each animal appeared in three of the five time blocks near the beginning, middle and end of the postinjection period..

Test sessions were initially conducted each 24 hours following saline injections until 5 days of control performance data were collected. Following the predrug control phase of the experiment UDMH, diluted 10 to 1 with distilled water, was administered intraperitoneally to each animal in doses of 4, 8, and 16 mg/kg body weight. Drug tests were conducted at 48-hour intervals with saline controls on alternate days.

SECTION III

RESULTS

Under normal conditions an animal negotiates the runway at stable velocities, demonstrating only a gradual decrease in speed as he becomes more satiated. Behavior does not change in relation to time of day. Previous studies have established the fact of long-term performance stability under normal conditions (Sterman and Fairchild, 1966). The mere introduction of UDMH into this test situation caused a general shift in performance during subsequent saline control measurements (Fig. 2). This residual effect of UDMH on control performance was not related to dose and the stability of controls during the course of the experiments indicated that UDMH had no cumulative effects. However, this alteration in control performance was a very real phenomenon since in four of the five animals there was a significant difference in predrug and postdrug control run times. These results are summarized in Table I.

Table I

Analysis of variance of control runway velocity data obtained before and after the initiation of UDMH testing.

Source	d.f.	Sum of Squares	Mean Square	F ratio
1) Cats	3	12.75	4.25	
2) Drug: Pre- vs Post-	1	1.41	1.41	470.0**
3) Trial Blocks	5	9.24	1.85	
4) 1 x 2	3	0.01	0.003	
5) 1 x 3	15	0.62	0.04	
6) 2 x 3	5	0.35	0.07	
7) Residual	15	0.13	0.01	
Total	47	24.51		

** $p = < 0.01$

Figure 2

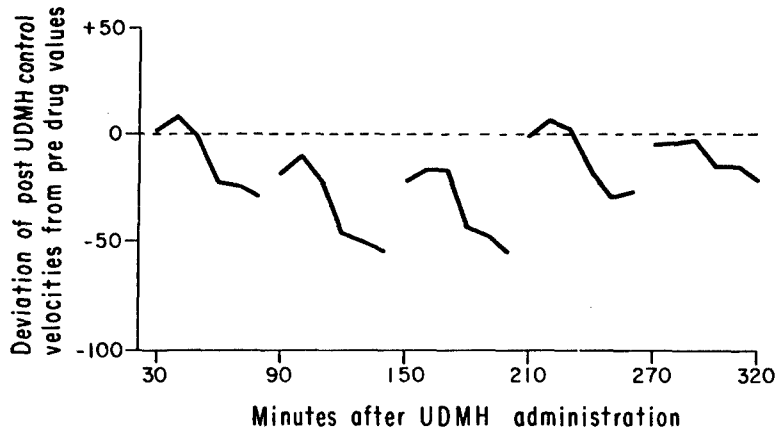

Figure 2: Comparison of saline control velocities obtained before and after the initiation of UDMH testing. The postdrug values are plotted here as deviations from their corresponding predrug levels. The data points represent the six trial block means of three different animals run in each of the five time periods after drug administration.

A possible explanation for this difference is apparent from a close inspection of Figure 2. Each curve in this figure is generated by the mean deviation from predrug saline control data of each of six sequential 10-trial blocks obtained from the three animals tested in a given time period. It can be seen that in every time period the deviation is progressively greater for the last three blocks of trials. This trend reflected an interaction between the normal reduction in velocity associated with increasing satiety and some residual influence of UDMH. Thus, in control measurements obtained 24 hours after the administration of low doses of this compound the slope of the normal satiety function is increased.

This effect is even more evident immediately after the administration of UDMH (Fig. 3). However, it is greatest in the first two time segments of measurement which cover a period up to 150 minutes postinjection. After 150 minutes, for doses of 4 and 8 mg/kg UDMH, there is a progressive reversal of effects, such that by 270 minutes animals receiving the two lowest doses often demonstrated maximum velocities during the last 30 trials of the test measurement. This change accompanied a more general shift in performance velocity associated with those doses at that time.

Figure 3

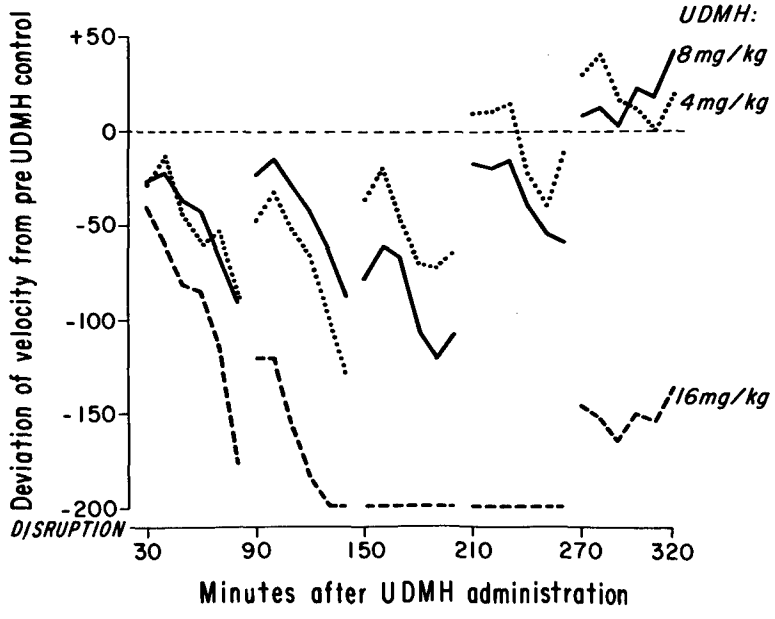

Figure 3: Comparison of performance after 4, 8, and 16 mg/kg UDMH with pretesting saline control data.

Since our primary concern was with these overall dose-time changes in velocity, the drug effects were subsequently expressed as deviations from the postdrug saline control values. The confounding caused by this interaction with satiety is thereby reduced because of a similar trend in the postdrug control data (Fig. 4). The interaction between satiety and UDMH was greatest during the earlier portion of the test period and thus, in spite of this

transformation of the data, it is still apparent in the 30 and 90 minute time blocks. Thereafter, the curves are flattened and indicate differential shifts in velocity in relation to the dose of UDMH administered.

Figure 4

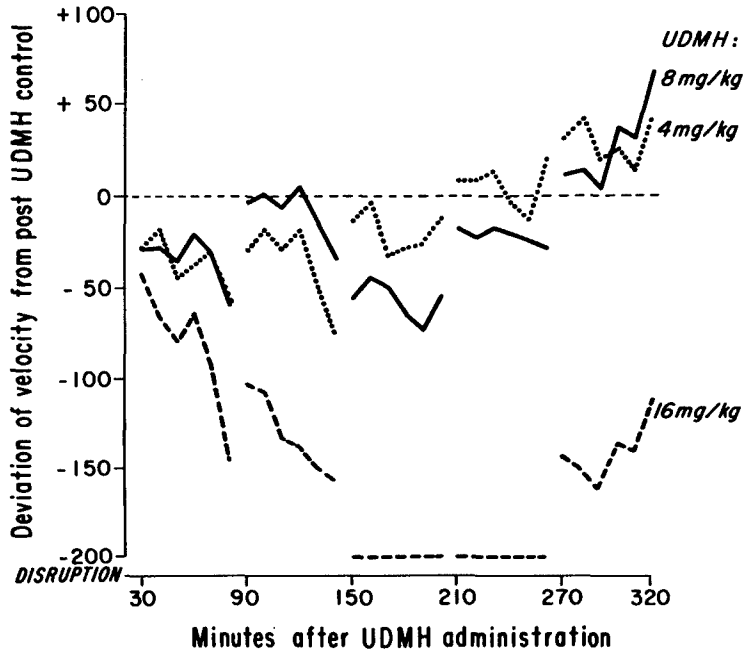

Figure 4: Comparison of performance after 4, 8, and 16 mg/kg UDMH with postdrug control data.

A statistically significant reduction in performance velocity was noted 30 minutes after the injection of 16 mg/kg UDMH, and became progressively increased until, by 150 minutes, behavior was greatly depressed or totally disrupted. This effect persisted for the next 2 hours. Performance was either relatively normal but extremely slow, or it was terminated by a consistent pattern of behavior. The cat stopped on the runway short of the goal box and refused to enter. At this point he would either sit and vocalize or groom, or he would turn around and approach the opposite chamber, only to stop again short of its entrance. The animal appeared apprehensive, was often disinterested in food, and showed a slight visual-motor incoordination. When

removed from the apparatus he would consume food eagerly and showed normal exploratory behavior. Visual motor coordination was still somewhat disrupted. This effect persisted for the next 2 hours. Variable results were obtained again in the last hour of the sequence, in that one animal remained disrupted, one animal was partially recovered, and the third was totally recovered. With the exception of an apparent disinterest in food and a slight visual-motor incoordination on the part of some of the animals, no emesis or other signs of distress were observed during the measurement period. Behaviorally the animals were occasionally irritable and somewhat hyperactive. In several instances a diarrhetic stool and intestinal residue were found in the home cage on the day following exposure at this dose level.

The administration of 8 mg/kg UDMH produced a complex effect upon runway performance. Initially, there was a moderate but significant reduction in velocity, followed by a recovery within the second hour. Performance was again depressed significantly during the third hour of measurement, but recovered once more in the succeeding hour. During the last test period, starting 270 minutes after injection, a reversal of effects was noted and indicated a reliable facilitation of performance. In two of the animals run during the third and fourth time periods after administration of 8 mg/kg, a disruption of performance identical to that described above for 16 mg/kg was noted during the last 10 or 20 runs of the session. These blocks were eliminated from the statistical treatment of data at this dose level.

The administration of 4 mg/kg UDMH exerted yet another characteristic effect upon subsequent runway performance. In this instance, velocity was mildly depressed 30 minutes after drug injection, but recovered gradually over the following two measurement periods. By 210 minutes postinjection, the animals were again running at normal velocities. However, in the last hour of measurement, a significant increase in velocity was registered.

Figure 5

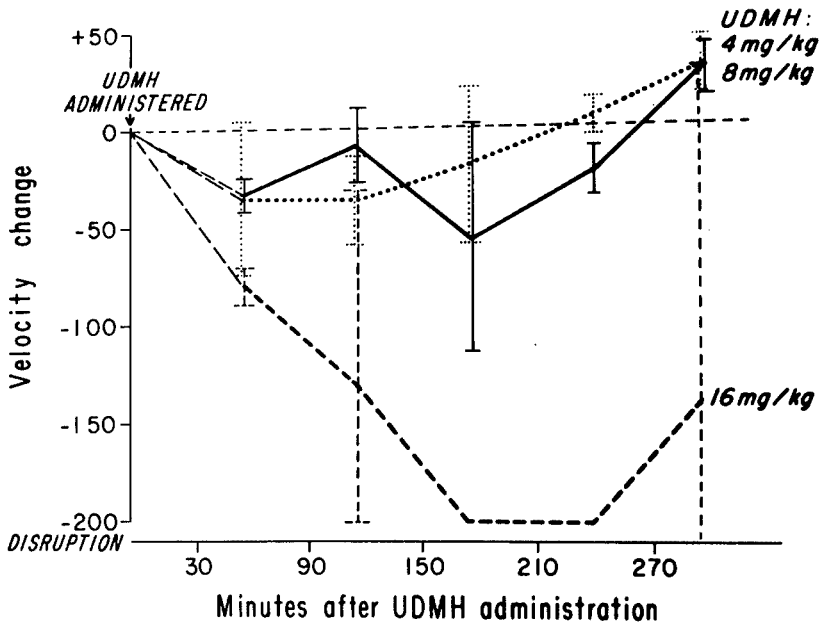

Figure 5: Summary of dose-time velocity alterations in response to three subconvulsive doses of UDMH. Each point indicates the mean of six blocks of ten trials each combined for the three animals run in a given time period after UDMH injection.

In order to more clearly visualize the various dose-time relationships reported above all data from the three animals run in each postinjection time period were combined and plotted together with the appropriate standard deviations in Figure 5. It can quickly be seen from this figure that the doses of 4, 8, and 16 mg/kg UDMH each had distinctive effects upon performance during the time span of experimental measurement. A dose of 16 mg/kg had a monophasic effect, with a gradual depression of velocity eventually reaching disruptive levels 3 to 4 hours after administration and diminishing in the last hour of measurement. The 8 mg/kg dose had a polyphasic influence on subsequent performance with a 2-hour cycle of depression and recovery followed by an enhancement of performance in the fifth hour after administration. Finally, 4 mg/kg caused a mild but protracted reduction in velocity which diminished gradually and gave way to an enhanced performance at the end of the measurement

period. In general, variability was greatest where the curves for the various doses were divergent and least where they converged. The statistical analysis of these data is presented in Table II.

Table II

Statistical comparison of velocity data obtained at the five time periods after saline or UDMH injection (N = 18).

Dose	Time Period (min.)	Mean	σ	t	Probability
4 mg/kg	30	-.35	.37	4.07	<.01
	90	-.37	.35	4.44	<.01
	150	-.19	.38	2.13	<.05
	210	+.05	.27	0.85	<.41
	270	+.30	.26	4.99	<.01
8 mg/kg	30	-.34	.24	6.01	<.01
	90	-.09	.27	1.41	<.18
	150	-.57	.53	4.51	<.01
	210	-.22	.21	4.52	<.01
	270	+.28	.30	3.99	<.01
16 mg/kg	30	-.81	.53	6.51	<.01
	90	-1.31	.92	6.06	<.01
	150	-2.12	1.14	7.92	<.01
	210	-2.48	.86	12.19	<.01
	270	-1.40	1.46	4.08	<.01

SECTION IV

DISCUSSION

Our previous experience with UDMH in the cat indicated that convulsions could occasionally be observed after a very long delay with doses as low as 20 mg/kg, but not with doses below that level (Fairchild and Sterman, 1965). For this reason we chose, in the present experiment, to deal with subconvulsive doses of 4, 8, and 16 mg/kg. We can now state clearly that these low doses can significantly alter the locomotor performance of this animal in a predictable manner, and without being accompanied by any other signs of UDMH toxicity. The performance alterations noted were found to be consistent for a given dose and different for each of the three doses tested. Furthermore, these effects were registered as soon as 30 minutes after the injection of this compound.

Within the postinjection time period covered in this experiment (6 hrs) the dose of 16 mg/kg UDMH produced a gradual disruption of performance followed by a tendency toward recovery in the last hour of measurement. There is no way of knowing what subsequent changes in performance might have occurred, but based upon the characteristics of response at lower doses and with other measures of CNS function, one could predict a continuing oscillation of decrement and recovery with a possible increment in performance after a protracted period of time. Indeed, such was the case for 8 mg/kg within the scope of the present experiment. A similar, but less complex pattern, was registered in response to 4 mg/kg, which consisted of a single mild decrement in performance followed after some delay by an increment. Although the animals tended to show a consistent pattern of response following a given dose of UDMH, it is apparent, from an inspection of Figure 5, that a large amount of individual variation exists. There is a tendency for variability

to increase with increasing drug effect, and, conversely, to decrease as drug effects abate. Increased variability with pronounced drug activity is particularly evident at 16 mg/kg, while decreasing variability with time is evident for both the 4 and 8 mg/kg dose levels. The relatively small standard deviations encountered for the period of enhanced runway performance following the lower doses of UDMH is of interest. In dealing with the relatively small number of animals tested in each time block (N = 3) normally distributed data would not be expected and large variations at peak drug effects would express interaction of UDMH with a number of individual differences in both physiological and behavioral parameters.

Exposure to UDMH was found to exert a general influence upon the course of satiety in our experimental situation, without causing any specific anorexic effects. The slope of the satiety function was markedly increased after all doses during the first two postinjection hours. This effect was still apparent, to a lesser degree, 24 hours after these injections. Visceral or central disturbances associated with the metabolism of this compound may be responsible for this apparent interaction between UDMH toxicity and the mechanisms underlying the process of satiation to food.

These findings represent the first stable performance data ever collected with UDMH experimentation in this laboratory. As such, they support our original contention regarding the characteristic variability encountered in previous behavioral studies of this compound. A systematic alternation of central depression and excitation, which these findings suggest is caused by UDMH, would confound any performance data obtained without a knowledge of its characteristics. We would propose that future attempts to evaluate the influence of UDMH on the performance of any specific task must consider this fact and incorporate its implications into the experimental design employed.

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13. ABSTRACT

Several recent neurophysiological findings in the study of 1, 1-dimethylhydrazine toxicity have suggested that this substance initiates a gradual increase in central nervous system (CNS) excitability, leading eventually to general convulsions. This process, however, is periodically interrupted by episodes of recovery or suppression of excitability. In the present experiment an attempt was made to investigate the nature of this alternation in response to low doses of UDMH, using the performance of a locomotor task as a measure of CNS effects. Cats were trained and tested in a special runway apparatus to provide a reliable indication of performance changes over a 6 hour period following the administration of 4, 8, and 16 mg/kg UDMH. These low doses significantly altered locomotor performance in a predictable manner. The response to a given dose was both consistent and unique to that dose. Within the 6 hour period of measurement, 16 mg/kg caused a gradual reduction in performance velocity leading to a total disruption, which was then followed by a tendency to recover; 8 mg/kg produced a recurrent depression of velocity followed by an enhancement, and 4 mg/kg resulted in a biphasic depression facilitation response. Other more general findings are also discussed.

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